Towards a European definition for a drug shortage: a qualitative study

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Abstract

Background: Drug shortages are currently on the rise. In-depth investigation of the problem is necessary, however, a variety of definitions for 'drug shortages' are formulated in legislations, by different organisations, authorities and other initiatives. For international comparison, the underlying definition for drug shortages is important to allow appropriate interpretation of national databases and the results of scientific studies. The objective is to identify the different elements which should be considered in a uniform definition for drug shortages in the European Union and to detect the different conditions for reporting drug shortages. Methods: Definitions of drug shortages were searched in the scientific databases as well as in the grey literature. Similar topics were identified and organisations were contacted to formulate the reasoning underlying the definitions. Results: Over 20 different definitions for drug shortages were identified. A distinction is made between general definitions of drug shortages and definitions used for the reporting of drug shortages. Differences and similarities are observed in the elements within the definitions, e.g. when does a supply problem become a drug shortage, permanent and/or temporally shortages, the typology and time frame of a drug shortage. The moment a supply problem is considered as a shortage, can be defined at four levels: (i) demand side, (ii) supply side, (iii) delivery of a drug and (iv) availability of a drug. Permanent discontinuations of drugs are not always covered in definitions for drug shortages. Some definitions only consider those drugs used for the treatment of serious diseases or drugs for which no alternative is available. Different time frames were observed, varying between one day and 20 days. Conclusion: Obtaining a uniform definition for drug shortages is important as well as identifying which conditions are preferable to report drug shortages in order to facilitate international benchmarking. This paper can be used as a guidance to point out all the different elements which should be considered to formulate a uniform definition to be applied in the European Union.

1 Introduction

Recently, drug shortages have become a common problem in European Union (EU) Member States (European Association of Hospital Pharmacists 2014). During the past decades, the awareness for drug shortages has been grown due to the observation of an increased number of drug shortages. Different stakeholders are engaged in the problem. In the first place, hospital as well as community pharmacies are affected by drug shortages. Patients are also troubled by this problem as well as medical doctors and nurses. They might be less familiar with the alternative treatment in case of a drug shortage, which can lead to medication errors (Heiskanen et al. 2014; Pharmaceutical Group of the European Union 2012; European Association of Hospital Pharmacists 2014; Yurukoglu 2012). Different umbrella organisations of the pharmaceutical industry published papers on drug shortages, some of them including guidelines on how to prevent and reduce risks for shortages. These actions suggest that drug shortages are also to the detriment of the pharmaceutical companies, due to the reputational damage it may provoke (European Federation of Pharmaceutical Industries and Associations 2013; ISPE 2014; European Association of Pharmaceutical Full-line Wholesalers (GIRP) 2013). National competent authorities are also burdened with the problem of drug shortages. Due to the EU Directive 2001/83/EC, national competent authorities should control the continue supply of drugs and should be warned by the suppliers of every cessation of pharmaceutical products whether this is temporally or permanently (De Weerdt et al. 2015).

Until recently, studies on drug shortages were mainly found in US literature (Ventola 2011; Kaakeh et al. 2011; Fox et al. 2014; Kweder and Dill 2013; Woodcock and Wosinska 2013). These studies investigated the scope, the causes and impact of drug shortages in the US. In recent years, more research concerning drug shortages in Europe has been published, trying to gauge the scope and causes of drug shortages (Pauwels et al. 2014; Heiskanen et al. 2014; Costelloe et al. 2014; Pauwels et al. 2015). However, the results of these studies are hard to compare as different definitions of drug shortages have been used.

Should a drug supply problem always be considered as a drug shortage or should it only be considered when patients have no longer access to a particular medicine? Are drug shortages taken into account when drugs cannot be delivered for only one day and thus should a time frame be considered in the definition of drug shortages? When manufacturers retract a product from the market, should it be considered as a drug shortage?

The objective of this paper is to identify the essential elements which are crucial in a definition for drug shortages and to identify which conditions are preferable to be considered when reporting drug shortages in databases. In order to achieve these aims, it was important to understand the reasons why certain organisations decided to develop their own drug shortage definition.

A uniform definition at EU level together with its reporting conditions will facilitate the problem of drug shortages at different levels. Firstly, international comparison will be facilitated, especially if the national databases of the reported drug shortages are publicly accessible. E.g. national competent authorities can easily control whether a drug shortage is an international or national problem. This information can also help them to find potential solutions. Secondly, the scope of drug shortages can be objectively estimated. Understanding the scale of the problem will help to take appropriate action against drug shortages by industry as well as national authorities. And thirdly, a uniform definition will also facilitate the communication between different stakeholders.

2 Methodology

Because the nature of the study, it was not required to seek approval from a research ethics committee. Data were analysed anonymously.

Data were collected in the scientific literature as well as in the grey literature between October the 6th 2014 and April the 31th 2015. Scientific articles were identified in the following databases: MEDLINE, Embase and Web of Science. The search strategy was developed incorporating synonyms for "drug shortages" combined with "defin*". By using an asterisk every word starting with "defin" was included. Individual search terms and MeSH search terms were used alone and in combinations. Studies published in English, French, Dutch and German were included in the paper. Additionally, the bibliography of the retrieved papers was checked for other relevant articles or studies. Grey literature, which are websites and documents of different stakeholders, was also searched for definitions of drug shortages. Some examples of possible sources which were searched for definitions are: legislations (e.g. Belgian law, EU Directives, etc.); governmental organisations (e.g. Italian Medicines Agency (AIFA), etc.), professional organisations (International Pharmaceutical Federation (FIP); European Hospital Pharmacists Associations (EAHP), etc.); patient organisations (e.g. European Public Health Alliance, etc.). The same language criteria as described above were applied to grey literature documents.

Definitions were analysed according to their literary differences and similarities. Main topics as: "the level of supply", "permanent or temporally discontinuation", "time limit" and "typology" were identified. These topics were investigated and observed differences and similarities were subdivided.

To identify the reasoning behind the wordings within the identified general definitions, the organisations and national authorities that formulated those definitions were contacted. Three main questions were asked: (i) "when should supply problems be considered as drug shortages? Should drug shortages include supply problems when patients are not affected (meaning: when patients have to switch to another (generic) medicine, they are affected)?"; (ii) "do you believe a time frame is important in the definition of a drug shortage? Please reason why"; and (iii) "Does the definition also include drugs which have been permanently discontinued? Please explain". These questions were sent via email to different organizations (seven national and four international). Answers were obtained from four national organizations and two international organizations. Appropriate quotes were selected from the answers and were translated from Dutch to English. Deleted parts of the quotes are indicated by "…". The coding [**R1, R2, etc.**] identifies the respondent.

3 Results

From the literature review twenty-six different definitions for drug shortages are identified ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015; Instituut voor Verantwoord Medicijngebruik 2012; The Italien Medicines Agency 2014; Food and Drug Administration 2011a; Government of Canada - Health Canada 2014; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; ISPE 2013; European Federation of Pharmaceutical Industries and Associations 2013; Charnay-Sonnek et al. 2013; Fédération Internationale Pharmaceutique 2013; Executive Agency for Health and Consumers 2012; Fox et al. 2009; Costelloe et al. 2014; Dragic 2012; Heiskanen et al. 2014; Pauwels et al. 2015; ANSM 2014; 'Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015; 'BfArM - Lieferengpässe' 2015; Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; Canadian Drug Shortage Database 2015; European Medicines Agency 2013). Different sources are acknowledged, including: national laws, governmental and professional organisations and scientific articles. All definitions found are unique, with the exception that most scientific articles refer to already existing definitions of the American Society of Hospital Pharmacies (ASHP) and/or the Food and Drug Association (FDA) (Becker et al. 2013; Wiggins et al. 2014; Balkhi et al. 2013). The definitions will be divided into three categories: (i) general definitions for drug or medicine shortages, (ii) definitions specifying the conditions to report drug shortages and (iii) definitions found in articles. It occurs that in some countries more than one definition is exploited: e.g. a definition for a drug shortage (national law) and a definition for the purpose of reporting a drug shortage (federal agency) (Food and Drug Administration 2011b; Fox et

al. 2009; Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; 'Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994).

The four definitions of drug shortages found in scientific articles will not be discussed in further detail, because the aim of these definitions is to clarify which shortages are covered by the scope of such paper.

In total 14 general definitions for drug shortages are found, including two references of national laws (Belgium and France), five of governmental organisations, six papers of professional organisations and a definition of the European Medicines Agency (EMA) which was formulated in 2014, however at the current time, that definition is removed from the EMA website ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015; The Italien Medicines Agency 2014; Instituut voor Verantwoord Medicijngebruik 2012; Food and Drug Administration 2011b; Fox et al. 2009; ISPE 2013; European Federation of Pharmaceutical Industries and Associations 2013; Executive Agency for Health and Consumers 2012; Fédération Internationale Pharmaceutique 2013; Charnay-Sonnek et al. 2013; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; Government of Canada - Health Canada 2014). An overview of these definitions can be found in Table 1.

Seven definitions of drug shortages for reporting purposes were found on websites of (inter)national authorities; one more was obtained by contacting the Royal Dutch Pharmacists Association Farmanco (Farmanco), the Dutch reporting database. Reporting websites are mostly nationally regulated, except for the database of EMA (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; 'BfArM - Lieferengpässe' 2015; 'Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015; ANSM 2014; Canadian Drug Shortage Database 2015; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; European Medicines Agency 2013; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014). Table 2 displays an overview of these eight definitions.

Remarkable differences between the definitions, such as "when do supply problems become drug shortages"; "permanent or temporally discontinuation"; "typology" and "time frame", will be discussed in further detail in the next subsections.

3.1 When do supply problems become drug shortages?

Not every supply problem immediately causes a drug shortage. In the definitions, diverse wordings are found to describe when supply problems become drug shortages. Shortages can be expressed in four different ways, specifically according to (i) the demand side (e.g. when the supply of a drug is inadequate to meet the current or projected demand), (ii) the supply side (e.g. interruption of supply), (iii) the delivery of a drug (e.g. undeliverable), and (iv) the availability of drugs (e.g. the availability of drugs to patients). Additionally drug shortages can occur at two different levels, namely (a) at pharmacies or wholesalers and (b) at consumers' level. The different expressions will be discussed in the next paragraphs.

Demand side - With respect to the demand side, the formulation: "when the supply of a drug is inadequate to meet the current or projected demand" is found in five general definitions, including the definitions of the FDA, International Society Pharmaceutical Engineering (ISPE), Australian Health Department, Health Canada as well as the definition found in the common position paper by Charnay-Sonnek *et al.* (see Table 1) and one definition for reporting purposes, namely of the Canadian Drug Shortages Database (see Table 2) (Food and Drug Administration 2011b; Government of Canada - Health Canada 2014; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; ISPE 2013; Charnay-Sonnek et al. 2013; Canadian Drug Shortage Database 2015). These wordings indirectly suggest that supply problems at pharmacy level (i.e. an

order that is not delivered) are not considered as drug shortages. As long as there is no demand for the drug which is experiencing supply problems, these organisations do not consider the situation as a drug shortage. The FDA, ISPE and the Australian Health Department complemented these wordings with "at patient/user/consumer level" (Food and Drug Administration 2011b; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; ISPE 2013; Charnay-Sonnek et al. 2013). A small difference should be acknowledged between "patient level" and "user or consumer level". The latter includes patients as well as healthy people using the drug, e.g. in experiments.

Supply side - Five definitions consider drug shortages at the level of the supply side using expressions as "inadequate supply", "interruption of supply" or "supply issue". Three out of the five are general definitions, namely from the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Dutch Institute for Rational Use of Medicines and the International Pharmaceutical Federation (FIP) (see Table 1) and additionally two reporting definitions: from the Federal Institute for Drugs and Medical Devices (BfArM) and Spanish Agency of Medicines and Medical Devices (AEMPS) (see Table 2) (Instituut voor Verantwoord Medicijngebruik 2012; European Federation of Pharmaceutical Industries and Associations 2013; Fédération Internationale Pharmaceutique 2013; 'Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015; 'BfArM - Lieferengpässe' 2015). These expressions do not indicate by whom, pharmacy or consumers, drug shortages should be perceived. Only the FIP indicates in the sequel of the definition that this supply issue impacts patient care (Fédération Internationale Pharmaceutique 2013).

Delivery of a drug - Definitions found in the Belgian and French laws, as well as the definition formulated by the EMA in 2014, use the phrase "undeliverable" as a basis for drug shortages (see Table 1) ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015). Again a difference is noticed regarding the specified level: the Belgian law declares a situation as a drug shortage at the level of community pharmacies, hospital pharmacies or wholesalers, while the French law and EMA specify their definitions at patient level ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015).

Availability of a drug - The Italian medicine agency (AIFA) and the Executive Agency for Health and Consumers (EAHC) define drug shortages as "the availability of drugs to patients" (see Table 1) (Executive Agency for Health and Consumers 2012; The Italien Medicines Agency 2014). This expression clarifies at which level drug shortages are considered, however it also regards access to medicines. The French National Agency for Medicines and Health Products Safety (ANSM) and the Federal Agency of Medicines and Health Products (FAMHP) use the expression of "unavailable" to specify the reporting conditions in France and Belgium (see Table 2) (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; ANSM 2014).

Considering the replies of the contacted organisations on the question: "when do supply problems become drug shortages", different opinions were observed. Answers are very divergent and the following quotes highlight the differences between several organisations on their approach to evaluating supply problems.

> *"All (supply) interruptions should be evaluated for their potential to contribute to a shortage." [**R1**]*

> *"Supply problems should be considered as drug shortages when the pharmacist or medical doctor has to change the prescription." [**R2**]*

*"A supply problem becomes a shortage as soon as it has consequences with regard to deliver medicines ..." **[R3]***

3.2 What about permanent discontinuation of drugs?

Drug shortages can be temporally (e.g. quality problems) or permanent (e.g. withdrawal of the marketing authorisation). As discussed above, diverse wording formulations are found to express drug shortages. Still it remains unclear for all of these expressions whether they include temporally as well as permanent discontinuation. After contacting different organisations, most organisations acknowledge the enormous consequences of permanent cessation of drugs, but do not consider it as a shortage, rather as an unavailability. The following quotes illustrate the different opinions:

*"If a manufacturer decides to permanent discontinue a drug, there are probably alternative treatments on the market" **[R2]***

*"The definition can imply the permanent discontinuation of a drug, because it means a shortage" **[R3]***

*"The definition would include drugs that have been permanently discontinued until medical and pharmacy practice change in response to the discontinuation. Until prescribers stop prescribing a specific drug product, pharmacists will still be addressing the lack of availability, regardless of cause." **[R4]***

3.3 Time frame

Three general definitions, namely from the Belgian and the French law and the Australian Health Department, incorporate a period during which the drug is unavailable. Only two of them indicate an exact time frame, both references are provided by national laws. The Belgian law declares "an uninterrupted period of four days" as time frame, while the French law defines drug shortages as situations where drugs are "undeliverable for three days" ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015). The Australian Health Department uses an undefined timeframe noting "not likely to meet the demand for a period of time" (Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015). It remains unclear when the Australian government will consider supply problems as a shortage; this period can range from one day to one month or even longer.

Most organizations agree that a time frame in a definition is superfluous, since it occurs that for instance in the northern part of a country a shortage is experienced while in the southern part the drug is still available.

*"In terms of a definition, then a time scale would seem to have little relevance." **[R1]***

*"... as soon as a pharmacist cannot deliver a prescription drug ... there is a shortage." **[R3]***

On the other hand, a specified time frame is often (in four of the eight definitions) used as a condition to report drug shortages (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Government of Canada - Health Canada 2014; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; 'BfArM - Lieferengpässe' 2015). Three databases will report shortages that go beyond 14 days, namely the FAMHP, Farmanco and BfArM ('BfArM - Lieferengpässe' 2015; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014). The Canadian drug shortages database reports only drug shortages which will take longer than 20 days (Government of Canada - Health Canada 2014). AEMPS uses an undefined time frame; they will report all shortages unless a rapid solution is expected ('Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015).

3.4 Typology

Including a time frame is one way to decrease the workload of (inter)national authorities when reporting drug shortages. Another way to decrease the workload of reporting drug shortages is by making a typology of the affected disease classes. This approach is only observed in reporting definitions and thus should be considered as a condition to report shortages. Databases of Germany and France will only report drugs which are intended for the treatment of life-threatening or serious diseases for which no alternative preparations are available (ANSM 2014; 'BfArM - Lieferengpässe' 2015). In Spain, Belgium, the Netherlands and Canada no explicit typology is included in the definition and thus all drugs experiencing supply problems will be reported ('Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015; Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; Government of Canada - Health Canada 2014).

4 Discussion

This study provides an overview of 26 unique definitions for drug shortages as provided by two legislations, five governmental organisations, seven professional organisations, four from scientific articles, seven national reporting databases and one European reporting database (see Table 1 and Table 2) ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994; 'Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015; Instituut voor Verantwoord Medicijngebruik 2012; The Italien Medicines Agency 2014; Fox et al. 2009; Food and Drug Administration 2011b; Government of Canada - Health Canada 2014; Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015; ISPE 2014; European Federation of Pharmaceutical Industries and Associations 2013; Charnay-Sonnek et al. 2013; Fédération Internationale Pharmaceutique 2013; Executive Agency for Health and Consumers 2012; Costelloe et al. 2014; Dragic 2012; Heiskanen et al. 2014; ANSM 2014; 'Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015; 'BfArM - Lieferengpässe' 2015; Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Canadian Drug Shortage Database 2015; European Medicines Agency 2013; Pauwels et al. 2015). A summary of the different elements in definitions is presented, accompanied by the conditions which are currently used to report drug shortages. The differences and similarities were compared and quotation marks with underlying reasons for a better understanding of the definitions were added.

Currently two types of definitions are in circulation: general definitions to designate a drug shortage and reporting definitions to specify when to report a drug shortage. This distinction is also implemented in the results section due to essential differences between the two types of definitions. However in the future, one should aim at aggregating both definitions into one to facilitate the comparison of reporting databases and scientific studies. A general definition should be developed to designate a drug shortage and additionally one must specify uniform conditions to report shortages. The general definition together with its reporting conditions should be developed in consultation with all stakeholders which are confronted with drug shortages and should be addressed to all different stakeholders. EU policy makers are best placed to set up a stakeholder forum where the main elements of the general definition together with its reporting definition can be discussed. We propose to include the definition and the reporting conditions in an EU Directive to reach more harmonized reporting databases based on the same definition, leaving the national authorities the responsibility on the means to achieve this goal.

To define this uniform definition for drug shortages, different decisions should be made. In the first place, one must determine which expression will be used to describe a drug shortage and at which level a drug shortage should be considered. At this moment four expressions are found: (i) when the supply cannot meet the demand, (ii) in case of an interruption of supply, (iii) when the drug is undeliverable, or (iv) when the drug is unavailable. Afterwards the level of drug shortages should be

determined. “At patient level” seems harder to identify in practice, while “an undelivered order” appears easier to detect. If the prices of drugs would be subjected to “free market” principles (i.e. a system in which prices for goods are set freely between vendors and consumers) a drug shortage, from an economic point of view, should be defined according to the demand side, because a shortage can only occur when the demand exceeds the supply (Simoens, Villeneuve, and Hurst 2005).

Whether to include permanent discontinuations is a third issue to be considered. Permanent discontinuations are subject to other rules in case of reporting the problem, therefore it might be easier to set proper conditions for temporary shortages and permanent ones (De Weerdt et al. 2015). Still it remains important to inform patients properly when a drug will be withdrawn from the market.

Incorporating a time frame in the general definition seems rather irrelevant for the following two reasons. First, only legislations contain time frames in their definitions. This can be explained by the necessity for the practical implementation of the legislations. Secondly, every country has its own policy on the delivery of drugs, therefore it might be hard to come to one time frame which can be generally applied. However, including a time frame as a reporting condition should be considered a feasible method to reduce the workload of the competent authority, especially since four of the eight references already included a specified time frame (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; Canadian Drug Shortage Database 2015; ‘BfArM - Lieferengpässe’ 2015). The three European references (Germany, The Netherlands and Belgium) specified that a drug should be in shortage for at least 14 days (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014; ‘BfArM - Lieferengpässe’ 2015), and perhaps this can be extended to all EU Member States’ databases.

Reducing the workload of competent authorities who are responsible for the drug shortages database can also be obtained by only including “drugs shortages which cause a risk for public health”. This is observed in Germany and France (‘BfArM - Lieferengpässe’ 2015; ANSM 2014). However, these restrictions will also misrepresent the size of the problem because not all shortages will be covered by the databases.

Differences between the found definitions of drug shortages can be partly explained by the diversity of stakeholders. Definitions in national legislations have other purposes than the definitions of drug shortages of professional organisations. This can be explained by the different roles, responsibilities and expectations of the different stakeholders. E.g. a time frame is found in national laws and not in definitions of professional organisations, probably because national legislations consider the specificities of the local drug market. However, this does not explain the differences within a group of the same stakeholders, which may be attributed to the different missions of the organisations. E.g. the definition of the European Federation of Pharmaceutical Industries and Associations (EFPIA) is very broad and will encounter a lot more drug shortages compared to the definition of the International Pharmaceutical Federation (FIP). Although the differences between and within stakeholders, the fact that so many organisations are troubled with this problem and searching for solutions, harmonisation on the definition of drug shortages at EU level seems possible.

A difference should be noted in the terms “drug shortage” and “drug unavailability”. A drug shortage is defined as “an interruption of supply chain”, while drug unavailability rather refers to “not introducing new, innovative drugs to the market” (De Weerdt et al. 2015). However, the Belgian federal agency denotes to *unavailability* instead of *shortage* and should be willing to reformulate its definitions in order to avoid confusion.

Obtaining a uniform definition for drug shortages is important as well as identifying which conditions are preferable to report drug shortages in order to facilitate international comparison. This paper can be used as a guidance to point out all the different elements which should be considered to formulate a uniform definition applied in the European Union. Nevertheless, the definition should acknowledge different national legislations and opinions of diverse stakeholders. The only way to obtain this is to sit

around the table with all stakeholders involved with supply problems, which should be the next step in this investigation.

5 List of abbreviations

AEMPS: Spanish Agency of Medicines and Medical Devices (Spain)
AIFA: Italian Medicines Agency (Italy)
ANSM: French National Agency for Medicines and Health Products Safety (France)
ASHP: American Society of Hospital Pharmacies (US)
BfArM: Federal Institute for Drugs and Medical Devices (Germany)
EAHC: Executive Agency for Health and Consumers
EFPIA: European Federation of Pharmaceutical Industries and Associations
EMA: European Medicines Agency
FAMHP: Federal Agency of Medicines and Health Products (Belgium)
Farmanco: Royal Dutch Pharmacists Association Farmanco (the Netherlands)
FDA: Food and Drug Association (US)
ISPE: International Society of Pharmaceutical Engineering
FIP: International Pharmaceutical Federation

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7 Authors' contribution

All authors participated in the design of the study. EDW performed data collection and analysis and drafted the manuscript. IH, SS, MC revised the manuscript critically and contributed to the interpretation of the data. All authors read and approved the final manuscript.

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10 Tables

Table 1: Overview of the general definitions of drug shortages

Source	Definition
Legislations	
Belgian law ('Wet Betreffende de Verplichte Verzekering Voor Geneeskundige Verzorging En Uitkeringen Gecoördineerd Op 14 Juli 1994' 1994)	A drug is unavailable when enterprises which are responsible for the marketing of the drug are unable to deliver that drug for an uninterrupted period of four days to the community pharmacies, hospital pharmacies or wholesalers in Belgium
On compulsory insurances for medical care coordinated on 14th July 1994 - art. 72 bis	
French law ('Décret N° 2012-1096 Du 28 Septembre 2012 Relatif À L'approvisionnement En Médicaments À Usage Humain' 2015)	A supply disruption is the inability for a dispensary pharmacy or internal use pharmacy dispensing a drug to a patient within 72 hours or within a shorter time depending on the compatibility problems with the continued treatment of the patient
Decree n° 2012-1096 the 28th of September 2012 on the supply of medicines for human use	
Governmental organisations	
Dutch Institute for Rational Use of Medicine (Instituut voor Verantwoord Medicijngebruik 2012)	The (temporally) not or inadequate supply of a registered pharmaceutical
Italian Medicines Agency (AIFA) (The Italien Medicines Agency 2014)	When a medicinal product is not available or commercially unavailable all over the country and the market authorisation holder does not assure appropriate and continued supply to meet the patients' needs
European Medicines Agency (EMA)	When the delivery of a medicine cannot comply to the needs of the patients, whether this is local, national or international
Food and Drug Agency (FDA) (Food and Drug Administration	A situation in which the total supply of all clinical interchangeable versions of a FDA-regulated drug is inadequate to meet the current or projected demand at the

2011b)	patient level
Health Canada (Government of Canada - Health Canada 2014)	A drug shortage is a situation when a manufacturer or importer of a drug cannot meet actual or projected demand. Drug shortages can include temporary disruptions or permanent discontinuances in the production and supply of a drug
Australian Ministry of Health (Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015)	A medicine shortage occurs when the supply of a medicine is not likely to meet the normal or projected consumer demand for the medicine within Australia for a period of time
Professional organisations	
International Society of Pharmaceutical Engineering (ISPE) (ISPE 2013)	A situation in which the total supply of an approved (by the appropriate Health Authority) drug is inadequate to meet the current or projected demand at the user level
European Federation of Pharmaceutical Industries and Associations (EFPIA) (European Federation of Pharmaceutical Industries and Associations 2013)	A potential drug shortage is defined as: the occurrence of internal or external situations (single or in a combination of both), which result in an interruption of supplies of a medicinal product, if not properly addressed and controlled
Common position paper (Charnay-Sonnek et al.) (Charnay-Sonnek et al. 2013)	A situation in which the total supply of an authorised medicine or of a medicine used on a compassionate basis is inadequate to meet the current or projected demand at the patient level. The shortage may be local, national, European or international
International Pharmaceutical Federation (FIP) (Fédération Internationale Pharmaceutique 2013)	A medicine shortage can be defined as a drug supply issue requiring a change. It impacts patient care and requires the use of an alternative agent
Executive Agency for Health and Consumers (EAHC) (Executive Agency for Health and Consumers 2012)	The availability to patients of medicinal products in a pharmacy setting
American Society of Hospital Pharmacies (ASHP) (Fox et al. 2009)	A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent

Articles	
Costelloe, *et al.* (Costelloe et al. 2014)	A drug shortage was defined as the inability to purchase a particular drug from wholesalers on a particular day
Dragic (Dragic 2012)	Drug shortage as every delay in monthly drug supply
Heiskanen, *et al.* (Heiskanen et al. 2014)	A drug supply issue requiring a change that impacts patient care and requires the use of an alternative agent
Pauwels *et al.* (Pauwels et al. 2015)	A shortcoming in the supply of a medicinal product that affects the patient's ability to access the required treatment in due time

Table 2: Overview of the reporting definitions of drug shortages

Source	Definition
National	
French National Agency for Medicines and Health Products Safety (ANSM) (ANSM 2014)	Drugs for which unavailability cause a risk for public health and have no therapeutic alternative
Spanish Agency of Medicines and Medical Devices (AEMPS) ('Agencia Española de Medicamentos Y Productos Sanitarios - AEMPS' 2015)	All drugs which experience supply problems are reported, except for those for which a rapid solution is expected
German Federal Institute for Drugs and Medical Devices (BfArM) ('BfArM - Lieferengpässe' 2015)	A supply shortage is expected to go beyond two weeks interruption extradition to the usual extent or a significantly increased demand that cannot be adequately met. Only supply shortages of drugs listed, where special information needs of professionals are required. Currently, this is for prescription drugs that are intended primarily for the treatment of life-threatening or serious diseases for which no alternative preparations are available
Belgian Federal Agency of Medicines and Health Products (FAMHP) (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten 2014)	Holders of the market authorisation should notify the Belgian Federal Agency of Medicines and Health Products (FAMHP) when a drug will be unavailable for a time period longer than 14 days
Royal Dutch Pharmacists Association Farmanco (Farmanco)	All supply problems of drugs are reported if it is expected that the drug will be undeliverable for a time period longer than 14 days

(Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014)	
Canadian Drug Shortage Databank (Canadian Drug Shortage Database 2015)	As soon as a market authorization holder knows that it will take longer than 20 days to supply a drug to meet expected patient volumes on an ongoing basis, they will report this as a shortage on the communications platform. It is understood that the inability of a patient to receive their prescribed medicines at the first attempt to fill a prescription may not constitute a drug being in 'shortage', as the drug may be available in other pharmacies or within the wholesale or distribution network (i.e. pharmacy supply chain), usually within a few days
Australian Medicine Shortages Information Initiative (Australian Government - Department of Health - Therapeutic Goods Administration (TGA) 2015)	This information is based on the voluntary notification by sponsors in accordance with the agreed Protocol
European	
European Medicines Agency (EMA) (European Medicines Agency 2013)	Medicines shortages that affect or are likely to affect more than one EU MS, where the EMA has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU